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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/638,648	08/14/00	STERN	D 0575/62097/J

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/638,648	Applicant(s) STERN ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the following species: 1) Subject to which the method will be administered: a) transgenic non-human animal and 2) Inhibitors for receptor for advanced glycation endproduct (RAGE): soluble RAGE, in Paper No. 6, is acknowledged.

Claims 1-16 are pending and being examined on the merits.

Drawings

The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81. No new matter may be introduced in the required drawing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a transgenic mouse which overexpress mutant human amyloid beta precursor protein (APP), bearing the double mutation Lys670Asn and Met 671Leu, (TG APP sw +/- mice) by administration of a soluble receptor for advanced glycation endproduct (sRAGE), the specification does not reasonably provide enablement for methods of decreasing cerebral vasoconstriction, ameliorating neurovascular stress or treatment of amyloid angiopathy in all transgenic non-human animals by administration of any inhibitor of RAGE. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a method for decreasing cerebral vasoconstriction in a subject suffering from chronic or acute cerebral amyloid angiopathy which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) to inhibit transcytosis of amyloid β (Aβ) peptides across the blood-brain barrier in the subject (claim 1). The claimed invention is further directed to a method for ameliorating neurovascular stress in a subject, comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 12). The claimed invention is additionally directed to a method of treating amyloid angiopathy in a subject comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 16). In particular, the elected inhibitor of

RAGE is soluble RAGE (sRAGE) and the elected subject is a transgenic non-human animal.

The specification teaches that administration of an inhibitor of RAGE can be used to treat subjects suffering from chronic or acute cerebral amyloid angiopathy, ameliorate neurovascular stress, or in the treatment of amyloid angiopathy (see p. 7. 1st paragraph, p. 8, paragraphs 1 and 3). The specification specifically teaches the blocking of RAGE in wild-type mice infused with synthetic amyloid-beta (Aβ) peptides by the use of an antibody against RAGE (α-RAGE), and soluble RAGE (sRAGE), which resulted in the suppression of binding and uptake of Aβ in relation to the vessel wall, and inhibited Aβ-induced cellular stress (see Example 1, and particularly p. 34). The specification teaches that Aβ transport to the brain was significantly inhibited by α-RAGE and abolished by sRAGE and that several other molecular reagents were used to test effects on blood brain barrier (BBB) transport or the binding of Aβ (see p. 32). The specification teaches that transgenic mice that overexpress mutant Aβ precursor protein (APP) (TG APP sw+/- mice) have a significant decrease in basal cerebral blood flow (CBF) values, and that infusion of α-RAGE increased the CBF in these mice. The specification teaches that systemic administration of α-RAGE to these transgenic mice ameliorated cellular stress in the brain (see p. 33, lines 11-29). The specification further teaches that an acute model in mice that had Aβ-induced cellular stress and sustained reductions in CBF was blocked by circulating α-RAGE, and in TG APP sw +/- mice, CBF was reduced by circulating α-RAGE in a dose-dependent fashion (see Example 2).

Although the specification does not explicitly teach the use of sRAGE administration to the TG APP sw +/- mice, Morser *et al.* (WO 97/39121, 23 October 1997) teach that both antibodies to RAGE and soluble RAGE are capable of blocking or inhibiting the interaction between RAGE and its ligands (AGEs) in such diseases as diabetes and Alzheimer's disease (see p. 9, 2nd paragraph and Examples 2 and 4). To this end, one would have a reasonable expectation of success in using sRAGE to increase CBF and ameliorate cellular stress in TG APP sw +/- mice. As such, the claimed invention is enabled for methods for decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a TG APP sw +/- mouse by the administration of sRAGE as indicated above.

However, the specification fails to teach methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in any other transgenic non-human animal other than the exemplified TG APP sw +/- mice. Additionally, the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic non-human animal as claimed, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce all transgenic animals which over-express mutant human Aβ precursor protein. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest; it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of

expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); *e.g.*, specific promoters, presence or absence of introns, *etc.* As such guidance is lacking in the instant specification, it fails to feature any correlation between the over-expression of a mutant human amyloid beta precursor protein transgene and/or mis-expression of the endogenous gene in any host animal, and, thus, a specific resulting disease phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human

growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of even one transgenic animal whose genome comprises a mutant human amyloid beta precursor protein transgene, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing an mutant human amyloid beta precursor

protein transgene, the levels of the transgene product, the consequences of that production, and therefore, the resulting phenotype.

With specific regard to claim 16, the claim encompasses treatment of amyloid angiopathy. Note that treatment encompasses complete amelioration of symptoms associated with Alzheimer's disease, and not necessarily a mere increase in cerebral blood flow, as such increase may not be sufficient to provide therapy in a subject with Alzheimer's disease, for example.

Accordingly, in view of the lack of guidance and direction in the specification for the use of sRAGE to decrease cerebral vasoconstriction or ameliorate neurovascular stress in any other species other than TG APP sw +/- mice, the lack of guidance or teaching for the treatment of amyloid angiopathy in such mice, the unpredictable and undeveloped state of the art with respect to transgene behavior in transgenic animals of all species, it would have required undue experimentation for one skilled in the art to carry out the claimed methods, animals and use thereof.

Conclusion

No claim is allowed. Claims 1-16 appear to be free of the prior art of record, in that the prior art of record fails to teach or suggest the use of sRAGE to decrease cerebral vasoconstriction, ameliorate neurovascular stress or treat amyloid angiopathy in a subject.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

TNT

Thaian N. Ton
Patent Examiner
Group 1632

JILL D. MARTIN
PRIMARY EXAMINER